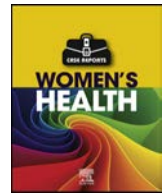




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## Pregnancy in a woman with recurrent immunoglobulin a nephropathy: A case report

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## ABSTRACT

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis and is increasingly encountered in pregnancy. The obstetric and renal outcomes of pregnancy are controversial, however. Women with IgAN are at higher risk of hypertension, preeclampsia and foetal loss; the prognosis is worse for those who have advanced chronic kidney disease and proteinuria. Here we report the case of a 32-year-old nulliparous woman with chronic hypertension who conceived during an active phase of her IgAN, which had been diagnosed 8 years earlier. Antihypertensive therapies and a low-protein diet were key to her reaching 34 weeks' gestation with acceptable kidney function. Rupture of membranes occurred at 34 weeks 3 days' gestation and a healthy boy was delivered the next day. This report aims to provide clinicians with useful information for the management of patients with IgAN during pregnancy.

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## 1. Introduction

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis, with a peak incidence in the second and third decades of life. It is caused by an aberrant glycosylation pattern of IgA1 and deposition of IgG-IgA immune complexes in the glomerular mesangium. A broad range of clinical manifestations are described, from minimal proteinuria to the development of end-stage renal disease (ESRD) [1,2]. The incidence of pregnancy in women with IgAN ranges from 26.6% to 61% [3]. Most pregnancies occur in patients with an established diagnosis. Though pregnancy does not seem to affect the long-term prognosis of patients with normal or slightly compromised renal function, especially in the absence of gestational hypertension [4], the risk of adverse obstetric outcomes is higher, with increased perinatal mortality (3% to 30%) and incidence of preeclampsia [5].

Proteinuria at the beginning of pregnancy has been reported to be strongly associated with severe preeclampsia and infant loss [3]. Pregnancy is known to be accompanied by physiological hyperfiltration, which may exert a negative effect on kidney function and increase proteinuria in patients with kidney disease [6]. For this reason, controlling proteinuria in pregnant women is often difficult, especially as most antiproteinuric agents (i.e., angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor inhibitors) are contraindicated during pregnancy.

Few cases of pregnancy during an active phase of IgAN have been described. Here, we report the case of a 32-year-old nulliparous woman with chronic hypertension who became pregnant during recurrence of IgAN diagnosed 8 years earlier.

## 2. Case Report

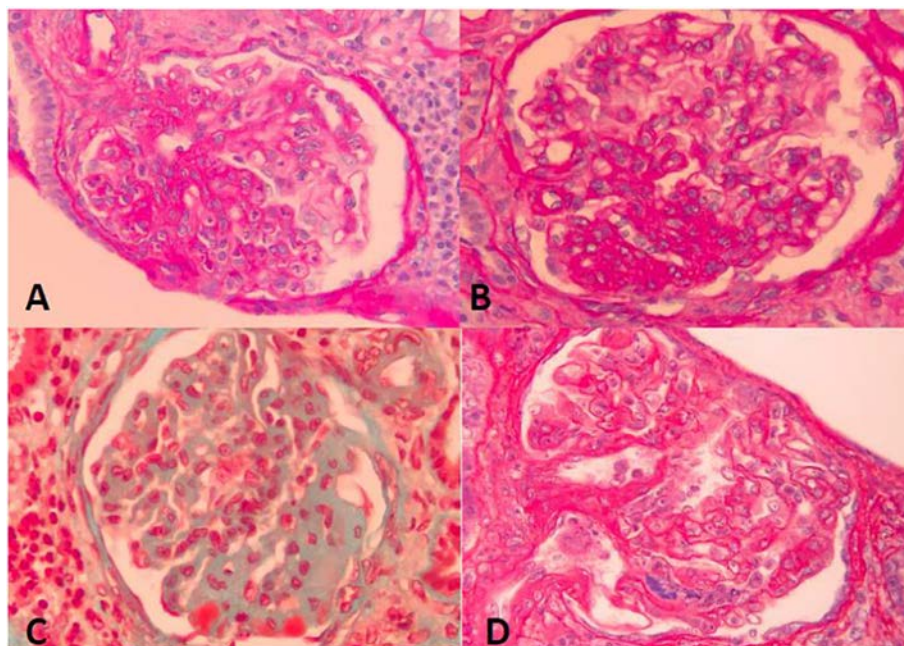
The patient first presented with persistent haematuria, fever and concomitant tonsillitis at the age of 24, for which she was hospitalised. The renal biopsy was considered insufficient for histological evaluation. She had proteinuria (protein level 2.6 g/dL), her creatinine levels ranged between 2.9 and 4.4 mg/dL, and haematuria was present. Based on clinical findings, a diagnosis of IgAN was made and treatment with steroids and azathioprine was initiated (100 mg a day). Regular follow-up continued for 4 years without further episodes of haematuria and with good blood pressure control (<120/80 mmHg).

At age 32 she was again hospitalised for haematuria. Renal ultrasonography revealed no kidney stones but moderately hyperechogenic renal cortex and medulla bilaterally (no previous scans were available for comparison). The serum creatinine level was 1.3 g/dL, albuminuria 300 mg/dL, and 24-h urine protein excretion 1.2 g. Her blood pressure was >140/90 mmHg. Given the patient's chronic hypertension, ACE-inhibitor therapy was started (enalapril 20 mg). When blood and urine analyses were performed 1 month later, the 24-h urine protein excretion was 2.2 g, serum creatinine 0.9 g/dL, creatinine clearance 85 mL/min and the red blood cell count was 30/50 cells per high-power field (HPF). A kidney biopsy was performed.

Microscopical analysis (Fig. 1 A–D) of periodic acid Schiff (PAS)- and trichrome-stained sections showed glomeruli with Bowman's spaces

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**Fig. 1.** (A) Segmental endocapillary proliferation (PAS stained section, 40×) (B) focal area of glomerular sclerosis (PAS stained section, 40×) (C) fibrinoid necrosis (trichrome stained section, 40×) (D) fibrinoid necrosis (PTAH stained section, 40×).

without crescents, normal-size mesangial regions, and thin and smooth capillary loops. In some segments, the capillaries were occluded by leukocytes or inflammatory cells (endocapillary proliferative glomerulonephritis) or showed fibrinoid necrosis and either segmental or global sclerosis. Specific stains (phosphotungstic acid haematoxylin [PTAH] and acid fuchsin orange G [AFOG]) highlighted deposits in the mesangial areas. Immunofluorescence revealed specific IgA and C3 deposits in the mesangial areas.

The diagnosis of IgAN was confirmed. Given the presence of active lesions and 24-h urine protein excretion >1 g, steroid therapy with intravenous methylprednisolone (1 g for 3 consecutive days followed by prednisone 0.5 mg/kg every other day) as described by Pozzi et al. [7] was initially planned. After taking the first dose of methylprednisolone, however, the patient tested positive on a self-administered urinary pregnancy test. Enalapril therapy was therefore immediately discontinued.

At 6 weeks' gestation, the patient's body weight was 60 kg, blood pressure 115/60 mmHg, serum creatinine level 1.1 mg/dL, 24-h creatinine clearance 70.6 mL/min and 24-h urine protein excretion 1.88 g. The patient stated she would continue the pregnancy. The steroid pulse regimen was discontinued. Treatment with prednisone 25 mg, omeprazole 20 mg, folic acid 5 mg, calcium 500 mg, omega 3 integrators daily, and supplementation with cholecalciferol (vitamin D3) (100,000 UI 25 drops weekly) was initiated. The patient checked her blood pressure daily and returned to the outpatient clinic every 2 weeks for blood and urine analysis.

At 16 weeks' gestation, 24-h Holter monitoring revealed an increase in blood pressure (>140/90 mmHg). Methyldopa (500 mg twice daily) was started and nifedipine (30 mg/day) added at 26 weeks' gestation due to the patient's elevated blood pressure. Antihypertensive treatment remained unchanged till delivery. Kidney function was closely monitored every 2 weeks for changes in serum creatinine and total 24-h urine protein excretion (Tables 1 and 2).

During the first 18 weeks of pregnancy, kidney function was stable, with a progressive decrease in serum creatinine to 0.8 mg/dL. An increase in 24-h urine protein excretion was observed starting at 20 weeks' gestation, with a peak of 1.8 g at 26 weeks, together with elevated blood pressure. Besides adjusting antihypertensive therapy, a low-protein diet supplemented with alpha-keto analogues and amino

acids was introduced to reduce animal-derived protein intake. The diet provided limited quantities (0.6 to 0.8 g/kg/day) and types of protein (plant-based diet, except for milk, yoghurt and butter), without any further restrictions and one to three unrestricted meals per week. For this regimen, the intake of any food of animal origin was discouraged, whereas plant-derived foods were allowed. To avoid excessive intake of sugar, the consumption of fruits in moderation was permitted, and to avoid excessive weight gain the patient was advised to limit the amount of food for the unrestricted meals. Supplements (Alfa-Kappa or Ketosteril) were prescribed (one tablet per 8–10 kg of body weight per day). Under this dietary regimen, 24-h urine protein excretion was successfully maintained at <1 g until delivery.

The patient remained asymptomatic during pregnancy, except at 24 weeks, when she started to show side-effects of corticosteroid therapy (increased blood pressure, weight gain, lunaris facies). Gestational diabetes was excluded by oral glucose tolerance testing (OGTT), and the prednisone dosage was reduced to 25/12.5 mg daily. An iron supplement was added to her dietary regimen due to persistently low haemoglobin values (10.6 g/dL). Ultrasound monitoring of foetal development was performed every 4 weeks. No major malformations were reported. Amniotic fluid, biometry and Doppler flowmetry of the uterine arteries and umbilical arteries were normal.

**Table 1**  
Kidney function and blood pressure up to 20 weeks' gestation.

Parameter	6 weeks	7 weeks +6 days	9 weeks +5 days	12 weeks	16 weeks	18 weeks	20 weeks
SBP/DBP	115/60	115/60	120/80	120/60	>140/90	140/90	140/90
SCr	1.1 mg/dL	0.9 mg/dL	0.9 mg/dL	0.8 mg/dL	0.8 mg/dL	0.8 mg/dL	0.8 mg/dL
24-h CrCl	72 <sup>a</sup> mL/min	66 <sup>a</sup> mL/min	97 <sup>a</sup> mL/min	126 <sup>a</sup> mL/min	–	–	172 <sup>a</sup> mL/min
24-h uP	1.8 g	1.1 g	1.6 g	1.4 g	0.9 g	0.9 g	1.1 g
RBC/HPF	5–10	10–15	>40	2–5	2–5		2–5

SCr denotes serum creatinine; 24-h CrCl 24-h creatinine clearance; 24-h uP 24-h urine protein excretion; RBC/HPF red blood cells/high-power field; SBP systolic blood pressure; DBP diastolic blood pressure.

<sup>a</sup> Corrected per 1.73 m<sup>2</sup>.

**Table 2**

Kidney function and blood pressure between 22 weeks' gestation and delivery at 34 weeks.

Parameter	22 weeks	24 weeks	26 weeks	28 weeks	30 weeks	32 weeks	34 weeks
SBP/DBP	130/80	130/85	>140/90	130/65	120/55	115/70	130/80
SCr	1.1 mg/dL	0.8 mg/dL	0.8 mg/dL	0.8 mg/dL	0.8 mg/dL	0.8 mg/dL	0.8 mg/dL
24-h CrCl	–	–	179 <sup>a</sup> mL/min	–	–	–	–
24-h uP	0.8 g	1 g	1.8 g	0.5 g	0.7 g	0.6 g	0.7 g
RBC/HPF	10–20	2–5	absent	2–5	5–10	2–5	2–5

SCr denotes serum creatinine; 24-h CrCl 24-h creatinine clearance; 24-h uP 24-h urine protein excretion; RBC/HPF red blood cells/high-power field.

<sup>a</sup> corrected per 1.73 m<sup>2</sup>.

At 32 weeks' gestation, the patient showed early signs of preterm labour. Routine obstetric examination revealed reduced cervical length, with initial cervical dilatation (approximately 1 cm). Ultrasound vaginal cervicometry showed a cervical length of 18.8 mm; an Arabin pessary was inserted. At 34 weeks and 3 days' gestation, preterm premature rupture of membranes (PPROM) occurred. The patient was hospitalised, received prophylaxis for foetal respiratory distress syndrome (12 mg of betamethasone repeated after 24 h) and antibiotic therapy. The next day a healthy male infant weighing 2660 g was delivered; the Apgar score was 9 at 1 and 5 min.

Ten days later, maternal renal function stabilised, with 24-h urine protein excretion 1 g and serum creatinine 0.9 mg/dL. The patient chose to discontinue breastfeeding. Her blood pressure was >140/100 mmHg. Methylodopa was replaced by enalapril 20 mg and prednisone was tapered over 15 days until total discontinuation. Her blood pressure was optimised to target levels (<140/90 mmHg) over 3 weeks. About 6 months later, renal function was stable. Blood and urine analysis showed 24-h urine protein excretion was 1.2 g, creatinine clearance 102 mL/min and red blood cell (RBC) count 3–5 RBC/HPF.

### 3. Discussion

Most large published series have included patients with a history of IgAN and excluded those with active disease. Different from a previously described case [8], this is the first report of pregnancy in an active phase of IgAN in a CKD patient with chronic hypertension. Our case report may provide useful information for clinicians (e.g., obstetricians, nephrologists) in the management of IgAN patients who become pregnant during re-activation of their disease.

Whilst the optimal management of IgAN remains uncertain, corticosteroid therapy may lower the risk of progression of kidney disease. Evidence on the treatment effects of other immunosuppressive agents is controversial [9]; their addition to therapy offers a potentially useful option in selected patients with a rapidly progressive clinical course [10]. We may speculate that administration of combined steroid/azathioprine therapy to the present patient after her initial hospitalization (not at our institution), in the absence of histological diagnosis, was motivated by rapidly progressive glomerulonephritis. Other studies suggest, however, that adding low-dose azathioprine or cyclophosphamide to corticosteroids does not give additional benefit to patients with IgAN [11,12]. Furthermore, immunosuppressive agents are not usually recommended in IgAN patients, except for those with crescentic IgAN with rapidly deteriorating kidney function.

In our patient the urine protein loss was >1 g per day, the serum creatinine level was 1.3–0.9 g/dL and the histological sample showed active lesions without crescents. Consistent with Italian national guidelines and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, she was treated with a combination of corticosteroids and antihypertensives [7,13]. Unexpectedly, she became pregnant whilst receiving high-dose steroid therapy plus an ACE inhibitor, which is

contraindicated during pregnancy due to the high risk of foetal toxicity and major congenital malformations.

The impact of IgAN on maternal and foetal outcome is controversial. A decline in kidney function, worse in advanced chronic kidney disease (CKD) [3,4], and a higher risk of superimposed preeclampsia (SPE) have been reported [5,14]. In their multicentre study on pregnancy and progression of IgAN, Limardo et al. reported a decline in kidney function in both the pregnancy and the non-pregnancy group, with initial proteinuria predicting a faster decrease [4]. Furthermore, pregnancies among patients with CKD stages 3 to 4 (estimated glomerular filtration rate [eGFR] < 60 mL/min), but not CKD stages 1 to 2, were associated with faster eGFR decline and an increased incidence of progression events [3]. Our patient became pregnant during an active phase of IgAN, as documented by renal biopsy (Fig. 1), and she could be categorized as having CKD stage 2 (eGFR 60–89 mL/min/1.73 m<sup>2</sup>) according to KDIGO guidelines.

The incidence of new-onset hypertension in normotensive women with IgAN prior to conception has not been associated with pregnancy [4]. Though this conclusion was reached in a study with one of the largest samples worldwide, such an event cannot be completely excluded. For example, an analysis of 12 Saudi women with well-controlled blood pressure prior to conception found that all of them required treatment for hypertension during pregnancy [5].

Our patient had chronic hypertension and showed progressive worsening of blood pressure starting from 16 weeks' gestation. Treatment with methylodopa 500 mg twice daily and nifedipine 30 mg once daily was administered, since patients with IgAN and chronic hypertension may, in fact, need aggressive treatment to control blood pressure. Such an approach, combined with the introduction of a low-protein diet, was effective in controlling 24-h urine protein excretion, which was reduced from 1.8 g to 0.5 g between 26 and 28 weeks' gestation.

Due to the increased risk of teratogenicity, administration of ACE inhibitors and angiotensin receptor inhibitors is contraindicated during pregnancy. Growing evidence supports the option of a low-protein diet for CKD patients since it has the potential advantages of controlling proteinuria and hyperfiltration. We counselled our patient on taking up a moderately protein-restricted “vegan-vegetarian diet”, as previously described by Attini et al., based on a protein intake of 0.6–0.8 g/kg/day, with one to three unrestricted meals per week (limited in unsaturated fats and short-chain sugars) and no specific restriction on salt, potassium or phosphate intake [15]. Poor pregnancy outcomes (e.g., small for gestational age and/or delivery before the 28th week) seem to be reduced in singletons from on-diet mothers, probably consequent to an improvement in the uteroplacental circulation. This could result from a decrease in so-called “vaso-toxic” elements and an increase in “vaso-protective” factors. Red meat consumption, which is associated with an increase in oxidative stress, is reduced; conversely, higher vegetable intake may protect against endothelial dysfunction [16].

A recent systematic review failed to find a consistent association between maternal vegetarian diet and newborn birth weight. Despite the lack of randomized studies powered to distinguish the effects of diet from confounding factors, vegan-vegetarian diets may be considered safe in pregnancy [17]. In this regard, the American Dietetic Association stated that “well-planned vegetarian diets are appropriate for individuals during all stages of the lifecycle, including pregnancy, lactation, infancy, childhood” [18]. To date, no studies have reported an increased risk of adverse pregnancy outcomes, except for an unexplained and unconfirmed report of a higher incidence of hypospadias in the children of vegan mothers [19]. Vegetarian diets may lack some nutrients that are essential during gestation (e.g., fatty acids, vitamin B-12, iron, zinc, and iodine) and possibly affect the baby's health. To avoid the development of dietary deficiencies, we regularly monitored iron, vitamin B12 and 25-OH vitamin D status; vitamins and iron supplements were added on the basis of blood chemistry results.



The aim of the low-protein supplemented diet was to reduce the workload on the nephrons, and it did in fact lead to a 24-h urine protein excretion under 1 g from 26 weeks till delivery. To our knowledge, this is the first time in which such an approach has been applied to a pregnant woman with IgAN.

Renal function, measured as 24-h creatinine clearance, improved from 72 mL/min to 96 mL/min (corrected per 1.73 m<sup>2</sup>) at 6 and 30 weeks' gestation, respectively. This increase is expected during pregnancy. Though renal function was not normal at the beginning of her pregnancy, it remained acceptable throughout. Progressive improvement was observed from 7 to 26 weeks' gestation, with a peak 24-h creatinine clearance of 179 mL/min.

Recently, infant loss has been closely associated with CKD stages: 19%, 23% and 45% in stages 1, 2 and 3 to 4, respectively [3]. CKD poses a challenge for managing pregnancy, from the early stages. Indeed, the rates of caesarean section, preterm birth and neonatal intensive care are higher than normal even at CKD stage 1. Hypertension and proteinuria are confirmed as independent risk factors. Preconception counselling and strict follow-up are advisable, even when renal function appears to be maintained at the beginning of pregnancy [20,21].

Despite the impact of CKD on pregnancy outcomes, conception is not contraindicated in patients with IgAN and CKD stages 1 to 2, whereas pregnancy in CKD stages 3 and 4 needs to be carefully considered [3]. Indeed, severe preeclampsia has been correlated with advanced CKD stages and proteinuria at the beginning of and during pregnancy is a significant risk factor for adverse outcomes. Proteinuria at conception has been independently associated with a faster decline in postnatal maternal eGFR. A reduction in urine protein levels (> 30%) prior to pregnancy is thus desirable in order to preserve kidney function [22]. Because the pregnancy was unexpected in our patient, it was impossible to reach this target and baseline 24-h urine protein loss was approximately 2 g before conception.

Our patient did not develop severe preeclampsia, though early signs of preterm labour were apparent at 32 weeks and PPROM occurred at 34 weeks. NICE guidelines consider women with a cervical length >15 mm at 30 weeks or more of gestational age to be at low risk of preterm birth [23]. In our patient, the cervical length was 18 mm and the dilatation was 10 mm at 32 weeks. After extensive discussion we decided to insert an Arabin pessary to delay the birth, possibly for a few weeks, although evidence for the benefits of pessary use at this gestational age is lacking. Among women who had asymptomatic singleton pregnancies and short transvaginal cervical length at 18 to 24 weeks, the use of cervical pessary, compared with no pessary, was associated with a lower rate of spontaneous preterm birth [24]. Nonetheless, the effectiveness of a cervical pessary for preventing spontaneous preterm birth remains debated [25] [26]. Our approach should be considered experimental because no data on pessary use at an advanced gestational age are currently available. Moreover, the risk of preterm labour and PPROM in IgAN patients has not been reported.

Women with PPROM have been noted to have mixed, abnormal vaginal microbiota [27]. Frequent causes of PPROM, such as urinary or cervicovaginal infections, were excluded by culture in the present case, but altered vaginal microbiota cannot be ruled out. Non-culture characterization of microbial communities by means of next-generation sequencing techniques, such as 16S ribosomal RNA (16S rRNA) gene sequencing, provides a much better understanding of vaginal microbial communities, whereas culture-based techniques vastly underestimate microbiome diversity [28]. Furthermore, there is emerging evidence that the diversity of vaginal microbiota during pregnancy correlates with preterm birth [29,30]. Whilst the effect of corticosteroid administration starting from early pregnancy on vaginal microbiota has never been explored, vegetarian diet has been associated with a different gut microbiome in early pregnancy, but the effects on the vaginal microbiota are unknown [31]. Further studies are needed to explore the possible impact of steroid treatments or alternative diets on vaginal

microbiota in pregnancy, especially when these approaches are used to treat chronic conditions such as IgAN or other nephropathies.

In conclusion, pregnancy in patients with recurrent IgAN and stage 1 or 2 CKD is not contraindicated if hypertension and renal insufficiency are controlled adequately. Close monitoring of renal function, blood pressure, genitourinary infections and foetal conditions is warranted to minimize the risk of hypertension, preeclampsia, preterm delivery and foetal loss.

Whilst therapy with high-dose steroids and ACE inhibitors in early pregnancy does not constitute an absolute contraindication to continue the pregnancy, the drugs must be discontinued as soon as possible. Prevention of proteinuria before and during pregnancy is strongly recommended, as it is one of the main risk factors for adverse outcomes. Pregnancy does not appear to be associated with a faster decline in renal function in these patients. Renal adaptation to pregnancy could result in a moderate improvement in 24-h creatinine clearance, at least in patients with recurrent IgAN in stage 1 or 2 CKD.

## Contributors

All authors contributed equally to the preparation of this case report and saw and approved the final manuscript.

## Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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## Consent

Informed, written consent was obtained from the patient.

## Provenance and Peer Review

This case report was peer reviewed.

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